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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/664,801	09/17/2003	Torben Halkier	4614-0120P	3913

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EXAMINER	
DEBERRY, REGINA M	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 03/16/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/664,801	HALKIER ET AL.	
	Examiner	Art Unit	
	Regina M. DeBerry	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *57-66* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *57-66* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/03,3/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Status of Application, Amendments and/or Claims

The amendment filed 29 January 2004 has been entered in full. Claims 1-56 are cancelled. New claims 57-66 were added. Claims 57-66 are pending and under examination.

Information Disclosure Statement

The information disclosure statement(s)(IDS) filed 17 September 2003 and 21 March 2005 were received and comply with the provisions of 37 CFR §§1.97 and 1.98. They have been placed in the application file and the information referred to therein has been considered as to the merits.

Sequence Rules

The specification is not in compliance with 37 CFR 1.821-1.825 of the Sequence Rules and Regulations. When the description of a patent application discusses a sequence listing that is set forth in the "Sequence Listing" in accordance with paragraph (c) of the Sequence Rules and Regulations, reference must be made to the sequence by use of the assigned identifier (SEQ ID NO:), in the text and claims of the patent application.

37 CFR 1.821(a) presents a definition for nucleotide and/or amino acid sequences. This definition sets forth limits in terms of numbers of amino acids and/or numbers of nucleotides, at or above which compliance with the sequence rules is

required. Nucleotide and/or amino acid sequences as used in 37 CFR 1.821 through 1.825 are interpreted to mean an unbranched sequence of four or more amino acids or an unbranched sequence of ten or more nucleotides. Please see MPEP section 2422.01.

The specification refers to a sequence on page 25, line 32, but does not identify the sequences by their sequence identifiers. Sequences appearing in drawings should be referenced in the corresponding Brief Description thereof. See 37 C.F.R. §1.58(a) and §1.83. Appropriate correction is required.

Appropriate correction is required. Applicant must submit a response to this Office Action and compliance with the sequence rules within the statutory period set for response to this Office Action.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 57, 60, 65 and 66 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 57 and 60 are incomplete for omitting essential steps; such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are a step, which recites the effective amount of an agent administered to down-regulate autologous OPGL.

Claim 65 recites the limitation "active immunization". There is insufficient antecedent basis for this limitation in claims 58, 59, 61 and 62, making the instant claim confusing.

Claim 66 recites the limitation "immunogenic agent". There is insufficient antecedent basis for this limitation in the claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 57-66 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

a method for down-regulation of autologous OPGL or treating, ameliorating a disease in an individual in need thereof comprising administering a polypeptide vaccine or a nucleic acid vaccine,

does not reasonably provide enablement for:

a method for **preventing a disease** in an individual **OR** administering a **live vaccine or a viral vaccine**.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The subject matter sought to be patented as defined by the claims is not supported by an enabling disclosure because the specification fails to teach how to

prevent a disease characterized by excessive bone resorption. Prevent means to completely stop a condition from occurring. "Prevention" is not a relative term, it is total. A very high degree of evidence is required, which is accepted in the art, that an absolute protection from the pathology exists over an extended period of time.

Secondly, the instant specification fails to teach how to administer a live vaccine and/or viral vaccine encoding OPGL. The examples from the specification teach the construction of OPGL protein vaccines. However, it could not be predicted that the instant data presented in the specification would be in any way correlative with administration of live and/or viral vaccines encoding OPGL. The specification states that an alternative for effecting presentation of modified OPGL to the immune system is the use of live vaccine technology. Presentation of the immune system is effected by administering to the animal, a non-pathogenic microorganism (attenuated bacterial strain; i.e. salmonella, mycobacterium), which has been transformed with a nucleic acid fragment encoding a modified OPGL or with a vector incorporating such a nucleic acid fragment. The specification states that as an alternative to bacterial live vaccines, the nucleic acid fragment of the invention can be incorporated in a non-virulent vaccine vector such as a vaccinia strain or any other suitable poxvirus. Medina *et al.* (Vaccine 19:1573-1580, 2001) teach the problems associated with the use of live bacterial carriers such as reversion to virulence, horizontal gene transfer, host genetic factor (see page 1577). The specification fails to teach immune responses, accommodation of heterologous DNA, safety concerns, lyophilization and/or host cell range of vaccine vectors. See Dudek *et al.* (Virology, 344:230-239, 2006). The disclosure provides no

guidance as to cloning the instant invention into the bacterial or viral vector. Dudek et al. teach that the major disadvantage to adenoviruses are that (with exception of HdAd vectors) they can only tolerate small heterologous sequences up to 9 kB. The disclosure fails to provide guidance regarding pre-existing immunity or safety. For example, Medina et al. teach that the possibility that prior exposure to the bacterial vector might compromise the efficacy of the initial or additional vaccine constructs has been demonstrated with salmonella. Dudek et al. teach that poxviruses are strong candidates for vaccine vectors but concerns about their safety still remain. The quantity of experimentation for the instant invention is not routine and the specification has provided little guidance on how to make and/or use the instant invention in a safe and effective manner.

Due to the large quantity of experimentation necessary to prevent a disease characterized by excessive bone resorption from occurring in a subject, the large quantity of experimentation necessary to generate live and/or viral vaccines encoding OPGL and screen same for activity, the lack of direction/guidance presented in the specification regarding same, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of live bacterial and viral vectors, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 57-66 are rejected under 35 U.S.C. 102(e) as being anticipated by Boyle, US Patent No. 5,843,678 (reference submitted by Applicant).

Boyle teaches the use of osteoprotegerin (OPG) binding proteins (i.e. OPGL) (column 2, lines 19-55 and column 3, lines 15-20). Boyle teaches that OPG binding proteins are involved in controlling the formation of mature osteoclasts, the primary cell type implicated in bone resorption. Boyle teaches that an increase in the rate of bone resorption can lead to various bone disorders such as osteoporosis (column 9, lines 45-50). Boyle teaches that agonists and antagonists of OPG binding protein modulate osteoclast formation and may be administered to patients suffering from bone disorders (column 9, lines 55-58). Boyle teaches that antibodies may be produced by immunization with OPG binding protein (column 7, lines 27-32). Boyle teaches that antibodies that bind to OPG binding protein and block interaction with other binding compounds may have therapeutical use in modulating osteoclast differentiation and bone resorption (column 7, lines 41-49). Boyle teaches pharmaceutical compositions comprising OPG binding protein and an adjuvant (column 7, lines 50-55 and claims).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 57-66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Anderson, US Patent No. 6,740,522 B2 in view of Tsukii *et al.,* Biochemical and Biophysical Research Communications 246:337-341 (1998).

Anderson teach that RANKL proteins are useful in augmenting an immune response such as a vaccine adjuvant (column 10, lines 51-62; column 15, lines 64-66 and claims). Anderson teach that DNA encoding RANKL can be used as an immunogen and such antibodies are useful in interfering with RANKL signaling; antagonistic or blocking antibodies (column 22, lines 44-50). Anderson teaches adjuvants (column 22,

lines 51-64). Anderson does not teach a correlation between RANKL and bone resorption.

Tsukii *et al.* teach osteoclast differentiation factor (ODF) as a ligand for osteoprotegerin (OPG) (abstract). Tsukii *et al.* teach ODF as being identical to RANKL (page 337, 2nd paragraph). Thus, RANKL is an OPG ligand. Tsukii *et al.* teach that OPG inhibits osteoclast development (inhibits resorption) *in vivo* (page 337, 1st-2nd paragraph). Tsukii *et al.* teach that *in vitro* bone resorption assays based on a bone tissue culture provides a system similar to the *in vivo* tissue microenvironment (page 338, 1st paragraph). Tsukii *et al.* teach that ODF induced bone resorption in fetal mouse long bone and antibodies against ODF suppressed bone resorption induced by various factors (page 339, Discussion). Tsukii *et al.,* who teach that antibodies against ODF inhibited bone resorption as effectively as OPG (page 340).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify a method of administering an immunogenic agent wherein in the agent is a RANKL nucleic acid vaccine as taught by Anderson to treat a disease characterized by excessive bone resorption with a reasonable expectation of success. The motivation and expected success is provided Anderson and Tsukii *et al.* Anderson teaches that DNA encoding RANKL can be used as an immunogen and such antibodies are useful in interfering with RANKL signaling; antagonistic or blocking antibodies. Tsukii *et al.,* who teach that antibodies against ODF (i.e. RANKL or OPGL) inhibit bone resorption as effectively as OPG.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Regina M. DeBerry whose telephone number is (571) 272-0882. The examiner can normally be reached on 9:00 a.m.-6:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda G. Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

RMD
3/12/06

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3/14/06